COMMONWEALTH of AUSTRALIA 629054
Patents Act 1952

APPLICATION FOR A STANDARD PATENT

I/We

N.V. Innogenetics S.A.

of

Industriepark Zwijnaarde 7, Box 4, Ghent, 9710, Belgium

hereby apply for the grant of a Standard Patent for an invention entitled:

Monoclonal antibodies directed against activated microglia cells, hybridomas secreting these monoclonal antibodies, antigen recognized by these monoclonal antibodies and their applications

which is described in the accompanying complete specification.

Details of basic application(s):-

Number	Convention Country	Date
89401932.2	Europe	5 July 1989

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this SECOND day of JULY 1990

To: THE COMMISSIONER OF PATENTS

.....
a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

Davies & Collison, Melbourne

AUSTRALIAN PATENT OFFICE LS

(CONVENTION. Company)

Form 5

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(1) Here insert (in full) Name of Company

In support of the Convention Application made by(1) N.V. INNOGENETICS S.A.

(hereinafter referred to as the applicant) for a Patent

(2) Here insert title of Invention.

for an invention entitled:(2)

"MONOCLONAL ANTIBODIES DIRECTED AGAINST ACTIVATED MICROGLIA CELLS, HYBRIDOMAS SECRETING THESE MONOCLONAL ANTIBODIES, ANTIGEN RECOGNIZED BY THESE MONOCLONAL ANTIBODIES AND THEIR APPLICATIONS"

(3) Here insert full Name and Address of Company official authorized to make declaration

I,(3) Paul J. Appermont
N.V. INNOGENETICS S.A.
of Industriepark Zwijnaarde 7
Box 4
9710 GHENT (Belgium)
do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

2. The basic application as defined by Section 141 of the Act was made in(4) Europe

on the 5th day of July 1989, by N.V. Innogenetics S.A.

on the ..... day of ..... 19 ..., by .....

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors

3.(5) 1/ GHEUENS Jan, Cottagelaan 43
8458 OOSDUINKERKE (Belgium)

2/ VAN HEUVERSWYN Hugo, Colmanstraat 62
9288 LAARNE (Belgium)

~~are~~ are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of of the said inventors in respect of the invention

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED

this 21st day of June 19..

(12) PATENT ABRIDGMENT (11) Document No. AU-B-58093/90
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 629954

(54) Title
MONOCLONAL ANTIBODIES DIRECTED AGAINST ACTIVATED MICROGLIAL CELLS, HYBRIDOMAS SECRETING THESE MONOCLONAL ANTIBODIES, ANTIGEN RECOGNIZED BY THESE MONOCLONAL ANTIBODIES AND THEIR APPLICATIONS

(51)[5] International Patent Classification(s)
C12P 021/08 C07H 021/04 C07K 015/12 C12N 015/12
G01N 033/577

(21) Application No. : 58093/90 (22) Application Date : 02.07.90

(30) Priority Data

(31) Number	(32) Date	(33) Country
89401932	05.07.89	EP EUROPE

(43) Publication Date : 10.01.91

(44) Publication Date of Accepted Application : 15.10.92

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(57) Claim

1. Monoclonal antibody which has the combination of the following properties:

- it forms an immunological complex with a non-phosphorylated epitope of an antigen belonging to activated microglial cells of the central nervous system and released from a sonicated NFT preparation, itself isolated from the cerebral cortex obtained from a patient having Alzheimer's disease,
- it forms an immunological complex with histiocytes and macrophages of the central nervous system.

25. Process for the detection or diagnosis in vitro of brain disease or brain infection involving activated microglia cells, such as Alzheimer's disease which comprises

- starting from a cell preparation, particularly NFT obtained from the cerebral cortex of a patient suspected of suffering neurofibrillar degeneration, e.g. Alzheimer's disease, whose nucleic acids have been made accessible to possible hybridization with other nucleic acids, whenever required,
- contacting said cell preparation or the nucleic acids previously extracted therefrom with the above defined

probe under suitable hybridization conditions, which possibly provide for the production of an hybrid between said probe and a sequence coding for said antigen and

- detecting the hybrid formed, if any, and assessing the possible existence or to the contrary absence of such neurofibrillar degeneration in said patient depending upon the occurence or not of hybridization.

27. A monoclonal antibody that forms an immunological complex with a non-phosphorylated epitope of activated microglial cells.

629954

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

NAME & ADDRESS OF APPLICANT:

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COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

Monoclonal antibodies directed against activated microglia cells, hybridomas secreting these monoclonal antibodies, antigen recognized by these monoclonal antibodies and their applications

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

The invention relates to new monoclonal antibodies involved in Alzheimer's disease, and to hybridomas secreting such monoclonal antibodies. It is also relative to an antigen which forms an immunological complex with one of said monoclonal antibodies. The invention also relates to a process for the diagnosis in vitro of brain diseases or brain infections, involving activated microglial cells.

The microglial cells are involved in the normal and pathological nervous system but their identification as well as their role is not yet known.

In fact, little is known about microglia. Since its description by Del Rio Hortega in Bol Soc Esp Biol 9, 69-120, its mere existence has remained a controversy. Some authors maintain that microglia is a specialized cell line resident in brain tissue, which differentiates into macrophages upon appropriate stimulation. For a more complete disclosure of this, one can refer particularly to :

- Boya J.J. Calvo A. Carbonell, E. Garcia-Maurino (1986) Nature of macrophages in rat brain, Acta Anat 127, 142-145,

- Boya J., J. Calvo, A.L. Carbonell (1987) Appearance of microglial cells in the postnatal rat retina. Arch. Histol Jap 50, 223-228

- Fujimoto E., A. Miki, H. Mizoguti (1987) Histochemical studies of the differentiation of microglial cells in the cerebral hemispheres of chick embryos and chicks. Histochem 87: 209-216

- Fujita S. (1980) Cytogenesis and pathology of neuroglia and microglia. Pathol Res Pract 168 : 271-278).

Other authors state that all macrophages in brain lesions are hematogenic (Hickey W.F., H. Kimura (1988) Perivascular microglia cells of the CNS are bone marrow-derived and present antigen in vivo. Science 239, 290-292). Classically, the microglial cell is described as a small cell with delicate ramifications, arising at nearly right angles (Dolman C., in Davis and Robertson, Textbook of Neuropathology). In some diseases microglia becomes elongated and gives rise to rod cells. In encephalitis, together with lymphocytes, they constitute microglial nodules. Pronounced microglial proliferation has been recognized in and around senile plaques in Alzheimer's disease (Terry R.D (1985), Alzheimer's disease in : R.L. Davis and D.M. Robertson, Textbook of Neuropathology, Williams and Wilkins, Baltimore pp. 824-841 - Terry R.D. Wisneiwski H.M. (1970) The ultrastructure of the neurofibrillary tangle and the senile plaque. In : Wolstenholme G. and O'Connor M. (eds) Ciba Foundation Symposium on Alzheimer's disease and related conditions).

The identification of microglial cells and assesment of their role in the normal and pathological nervous system has been hampered by lack of a specific staining technique. The silver impregnation technique described by Del Rio Hortega not only stains microglia but also oligodendroglia and some astrocytes (Ganter et J Jollès (1969) Histochimie. Gauthier Villars, Paris, pp. 1463-1466). Microglia can be immunolabelled with different antibodies, some of which also react with circulating macrophages (Esiri M. M., J. Boss (1984) Comparison of methods to identify microglial cells and macrophages in the human central nervous system. J. Clin Pathol 37, 150-156 - Vazeux R., N. Brousse, A.

Jarry, D. Henin, C. Marche, C. Vedrenne, J. Mikol, M. Wolff, C. Michon, W. Rozenbaum, J.F. Bureau, L. Montagnier, M. Brahic, (1987) AIDS subacute encephalitis. Identification of HIV-infected cells. Am J Pathol 126, 403-410). However, these antibodies are not specific to microglial cells, and they can only be applied on cryosections, with exception of some anti-HLA-DR antibodies that can be used on paraffin embedded material (Vazeux, see above mentioned reference). Microglia and macrophages have also been stained with antibodies directed to α_1-antichymotrypsin, lysozyme and α_1-antitrypsin (Esiri, see above mentioned reference). Some reactive cells of possible microglial origin can be demonstrated in the central nervous system with histochemical stainings for acid phosphatase and non-specific esterase (Bancroft J.D. (1975) Histochemical techniques. 2nd ed London, Butterworth, p. 254). Recently, Ricinus communis agglutinin type-1 (RCA-1) has been used to stain cells with the morphology of microglia (Mannoji H., H. Yeger, L.E. Becker (1986) A specific histochemical marker (lectin Ricinus communis agglutinin-1) for normal human microglia and application to routine histopathology. Acta Neuropathol (Berl) 71, 341-343). This lectin, specific for a lactose moiety, can be used on paraffin embedded formalin fixed material. However, RCA-1 staining is not specific for microglia, since endothelial cells are also stained.

Up to now, there was no way of specifically detecting microglial cells, and in particular to distinguish them from other cells such as oligodendroglia, astrocytes and endothelial cells.

The aim of the invention is to provide with monoclonal antibodies which enable to specifically detect activated microglial cells.

The invention also provides with hybridomas secreting the above said monoclonal antibodies.

The invention provides with an antigen which is expressed in a subpopulation of microglial cells reactive to various pathologic conditions.

The invention provides with a process for the detection or diagnosis in vitro of brain diseases involving activated microglial cells, e.g. brain tumors, brain infections, AIDS, Alzheimer's disease.

A monoclonal antibody of the invention is characterized by the fact that it forms an immunological complex with the syngeneic polyclonal anti-idiotypic serum raised against the monoclonal antibody secreted by the hybridoma deposited at the C.N.C.M. under n°I-881 on July 5, 1989 (AMC30 IgM) or by the hybridoma deposited at the C.N.C.M. under n°I-882 on July 5, 1989 (AMC30 IgG).

A monoclonal antibody of the invention is characterized by the fact that it forms an immunological complex with the monoclonal anti-idiotypic antibody raised against the monoclonal antibody secreted by the hybridoma deposited at the C.N.C.M. under n°I-881 on July 5, 1989 (AMC30 IgM) or by the hybridoma deposited at the C.N.C.M. under n°I-882 on July 5, 1989 (AMC30 IgG).

The monoclonal antibodies of the invention are defined through their idiotype. Idiotypes are sets of idiotopes, i.e. a collection of individually specific antigenic determinants of immunoglobulins (in contrast to allotype and isotype), and can therefore be considered to be a "fingerprint" of an antibody. For full disclosure of idiotype and anti-idiotype, see e.g. de Préval C: Immunoglobulins, p. 144-219 in Bach J.F.: Immunology, Publ. Wiley and Sons, new York, 1978 or Fleischmann J.B., Davie J.M.: Immunoglobulins: allotypes and idiotypes, pp. 205-220 in Paul

W.E.:Fundamental Immunology, Publ. Raven Press, New York, 1984. The monoclonal antibodies of the invention specifically react with the anti-idiotypic serum raised against the monoclonal antibody secreted by the hybridoma deposited at the C.N.C.M. under n°I-881 on July 5, 1989 (AMC30 IgM) or by the hybridoma deposited at the C.N.C.M. under n°I-882 on July 5, 1989 (AMC30 IgG), in BALB/c mice in syngeneic conditions. Other BALB/c monoclonal antibodies, of whichever class, subclass or type, fail to react with said syngeneic serum to the monoclonal antibody secreted by the hybridoma deposited at the C.N.C.M. under n°I-881 on July 5, 1989 (AMC30 IgM) or by the hybridoma deposited at the C.N.C.M. under n°I-882 on July 5, 1989 (AMC30 IgG), thus demonstrating the idiotype-specific character of the syngeneic antiserum.

The syngeneic polyclonal anti-idiotypic serum raised against the monoclonal antibody of the invention is obtained by immunization of an animal with a monoclonal antibody of the invention which is raised in a syngeneic, i.e. genetically identical animal, said syngeneic polyclonal serum raised against a monoclonal antibody of the invention containing no other anti-immunoglobulin antibodies than the anti-idiotypic antibodies.

The syngeneic polyclonal anti-idiotypic serum raised against a monoclonal antibody of the invention enables to identify said monoclonal antibody, particularly because said syngeneic polyclonal anti-idiotypic serum does not select for public idiotopes and contains high titers of anti-idiotypic antibodies to private idiotopes of the monoclonal antibodies and particularly because said syngeneic polyclonal anti-idiotypic serum contains and defines the whole set of idiotopes.

The methods used for production of syngeneic anti-idiotypic serum to monoclonal antibodies have been described before (Gheuens J., McFarlin D.E., Rammohan K.W., Bellini W.J.: Idiotypes and biological activity of murine monoclonal antibodies against the hemagglutinin of measles virus, Inf. Immun. 34: 200-207, 1981; Bona C., Hooghe R., Cazenave P.A., Leguern C., Paul W.E.: Cellular basis of regulation of expression of idiotype II. Immunity to anti-MOPC460 iditoype antibodies increases the level of anti-trinitro-phenyl-antibodies bearing the 460 idiotypes. J. Exp. Med. 149:815-823, 1979).

The methods for production of monoclonal anti-idiotypic antibodies have been fully described (Gheuens J., MacFarlin D.E.: Use of monoclonal anti-idiotypic antibody to P3-X63Ag8 myeloma protein for analysis and purification of B lymphocyte hybridoma products. Eur. J. Immunol. 12:701-703, 1982).

A monoclonal antibody according to the invention is defined by the combination of the following properties:

- it forms an immunological complex with a non-phosphorylated structural epitope of an antigen belonging to activated microglial cells of the central nervous system and released from a sonicated NFT preparation, itself isolated from the cerebral cortex obtained from a patient having Alzheimer's disease,
- it forms an immunological complex with histiocytes and macrophages in the vicinity of necrosis areas in the central nervous system.

The expression "structural epitope" refers to an epitope defined by the primary structure, but not the conformation of the antigen. In other words, this epitope is preserved even after treatment of the antigen in ways that will alter its conformation, such as fixation of the antigen with formalin,

glutaraldehyde or paraformaldehyde, and after denaturation of the antigen preparation with ionic and non-ionic detergents.

The expression "non phosphorylated epitope" means that the epitope of the antigen to which the monoclonal antibodies of the invention bind are not phosphorylated, as determined by the following test, which comprises :

- starting from an NFT-enriched fraction prepared as described (Iqbal K, Zaidi T, Thompson CH, et al. Alzheimer paired helical filaments: bulk isolation, solubility and protein composition. Acta Neuropath. 1984; 62:167-177), immunoblotted to nitrocellulose as described above and treated overnight at 37°C with 1 IU of Type III E.coli alkaline-phosphatase, in 100ml 0.1M Tris buffer, pH8.0, containing 0.01M phenyl-methyl-sulfonyl-fluoride, applying one of the monoclonal antibodies of the invention to said NFT, forming an immunological complex between NFT and the monoclonal antibody.

The expression "activated microglial cells" refers to a microglial cell that has differentiated from the "resting" state to an "active" state under the influence of a pathological process in its vicinity. The precise nature of the cell biological processes that comprise this transition from "resting" to "active" are not yet defined, and the term "activated microglial cell" hence is a purely operational definition at this time.

The expression "antigen belonging to activated microglial cells" means antigen expressed in micrcglial cells in the vicinity of a pathological process in the central nervous system, or in microglial cells that participate in a systemic pathological process, but not expressed in microglial cells in the normal central nervous system.

The expression "form an immunologically complex with" means that the monoclonal antibody of the invention binds to the abovesaid antigen under one in the following conditions in the following techniques.

- Light immunomicroscopy:

Brain tissue sample, obtained at surgery or autopsy, was fixed by immersion in 4% formalin or Bouin's fixative and embedded in paraffin. Four mm thick sections were prepared. The monoclonal antibody of the invention was applied either with the avidinbiotinylated peroxidase complex technique (Hsu SM, Raine L, Fanger H. Use of avidinbiotin complex (ABC) in immunoperoxydase techniques. J. Histochem. Cytochem. 1981; 29:577-580), or with the soluble peroxidase-anti-peroxidase complex technique (Sternberger LA, Immunocytochemistry (3rd ed.). Wiley, New York, 1986).

Diaminobenzidine was used as chromogen.

- Immunoelectron microscopy in tissue sections:

Brain tissue sample, obtained at surgery or autopsy is fixed in either Bouin's fixative or 10% buffered formalin before sectioning 60mm thick without embedding (Vibratome). The sections were immunostained by the indirect immunogold method, fixed, embedded and sectioned for electronmicroscopy as described (Perry G, Mulvihill P, Manetto V, et al. Immunocytochemical properties of Alzheimer straight filaments. J. Neurosci. 1987; 7:3736:3738).

- Immunoblotting procedures:

Fractions enriched in PHF, prepared as described (Iqbal K, Zaidi T, Thompson CH, et al. Alzheimer paired helical filaments: bulk isolation, solubility and protein composition. Acta Neuropath. 1984; 62:167-177) were sonicated and used as samples in SDS-polyacrylamide electrophoresis and immunoblots. SDS-polyacrylamide electrophoresis was done under reducing

conditions on 12% gels (Laemmli UK. Cleavage of structural proteins during the assembly of bacteriophage T4. Nature 1970;227:680-685). After electrophoresis, the proteins were either fixed and stained with Coommassie brilliant blue, or transferred (Towbin H, Staehelin T, Gordon J. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. Proc. Natl. Acad. Sci. USA 1979;76:4350-4354) to nitrocellulose (Hybond-C, Amersham) or Immobilon filters (Millipore). After transfer the filters were presoaked in PBS containing 0.05% (v/v) Tween 20 (Tween-PBS) and then incubated for 1h in Tween-PBS containing 5% (w/v) skimmed dried milk and 5% (v/v) normal goat serum (blocking buffer). Next, the filters were treated overnight at 4°C with primary antibody appropriately diluted in blocking buffer. The filters were then washed three times in Tween-PBS and treated for 1 1/2h at room temperature with biotinylated goat anti-mouse IgM (Amersham) diluted 1/250 in blocking buffer. After three washes in Tween-PBS, streptavidine-biotinylated horseradish peroxidase complex (Amersham) diluted 1/250 in blocking buffer was applied for 1 1/2h at room temperature. Afterwards, the filters were washed three times in Tween-PBS and once in PBS, The filters were then incubated in PBS containing 0.0.5% (w/v) diaminobenzidine and 0.01% (v/v) hydrogen peroxide until background staining developed.

It should be clear that the formation of an immunological complex between the monoclonal antibody and the antigen is not limited to the precise conditions described above, but that all techniques that respect the immunochemical properties of the antibody and antigen binding will produce similar formation of an immunological complex.

The "histiocytes" and the "macrophages of the central nervous system" are defined in Greenfield's Neuropathology, and other classical textbooks on neuropathology.

A monoclonal antibody of the invention is characterized by the fact that it forms an immunological complex with the syngeneic polyclonal anti-idiotypic serum, particularly the monoclonal anti-idiotypic antibody, raised against the monoclonal antibody secreted by the hybridoma deposited at the C.N.C.M. under n°I-881 on July 5, 1989 (AMC30 IgM) or by the hybridoma deposited at the C.N.C.M. under n°I-882 on July 5, 1989 (AMC30 IgG) and by the combination of the following properties:

- it forms an immunological complex with a non-phosphorylated structural epitope of an antigen belonging to activated microglial cells of the central nervous system and released from a sonicated NFT preparation, itself isolated from the cerebral cortex obtained from a patient having Alzheimer's disease,

- it forms an immunological complex with histiocytes and macrophages in the vicinity of necrosis areas in the central nervous system.

A particular preferred monoclonal antibody is of the IgM class, kappa type, or of the IgG, kappa type.

Advantageously, the monoclonal antibodies of the invention have the following properties :

- they do not bind immunologically with resting microglial cells of the central nervous system in pathological conditions,

- they do not bind immunologically with resting macrophages of organs other than the central nervous system,

- they do not bind immunologically with neurofibrillary tangles or amyloïd,

XP-002137345

AN - 1991-058319 [09]
AP - AU19900058093 19900702; EP19900401836 19900626; JP19900178472 19900705
CPY - INNO-N
CT - 4.Jnl.Ref
DC - B04 D16 S03
DS - AT BE CH DE ES FR GB GR IT LI LU NL SE
FS - CPI;EPI
IC - C07H21/04 ; C07K15/12 ; C12N5/20 ; C12N15/12 ; C12P21/08 ; C12Q1/68 ; G01N33/57
IN - GHEUENS J; VANHEUVERS H
MC - B04-B04A1 B04-B04C2 B04-B04C5 B04-B04H B11-C07A B12-K04A1 B12-K04A4 B12-K04A5 D05-H06 D05-H07 D05-H09 D05-H11
- S03-E14H4
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- [02] M423 M424 M710 M740 M760 M903 N102 Q233 V754
- [03] M423 M424 M710 M740 M750 M903 N102 Q233 V791
- [04] M423 M424 M740 M750 M903 N102 Q233 V500 V560 V753
M6 - [05] M903 P831 Q233 R501 R515 R521 R614 R621 R631 R635
PA - (INNO-N) INNOGENETICS SA
PN - AU5809390 A 19910110 DW199109 000pp
- EP0415801 A 19910306 DW199110 000pp
- CA2020543 A 19910106 DW199113 000pp
- JP3058797 A 19910313 DW199117 000pp
PR - EP19890401932 19890705; EP19900401836 19900626
XA - C1991-024653
XIC - C07H-021/04 ; C07K-015/12 ; C12N-005/20 ; C12N-015/12 ; C12P-021/08 ; C12Q-001/68 ; G01N-033/57
XP - N1991-045227
AB - AU9058093 Novel monoclonal antibody (I) has the following characteristics: (a) it forms an immunological complex with a non-phosphorylated epitope of an antigen, belonging to activated microglial cells of the central nervous system (CNS), and released from a sonicated NFT prepn., itself isolated from the cerebral cortex obtd. from a patient with Alzheimer's disease; and (b) it forms an immunological complex with histiocytes and macrophages of the CNS. (I) also forms (separately claimed) an immunological complex with the syngeneic polyclonal anti-idiotypic serum, partic. with the monoclonal anti-idiotypic antibody, raised against the monoclonal antibody (II) secreted by the hybridoma deposited at the CNCM under No. I-881 (AMC30 IgM) or by the hybridoma deposited at the CNCM under No. I-882 (AMC30 IgG).
- (II) is claimed per se.
- Also claimed is a monoclonal antibody which forms an immunological complex with an antigen released from a sonicated NFT prepn. isolated from the cerebral cortex of a patient with Alzheimer's disease, which antigen itself forms an immunological complex with (II). Antigens corresp. to the claimed monoclonal antibodies are also provided. Specifically (I) is of the IgM class, kappa type or of the IgG kappa type.
- USE - (I) are useful for in vitro diagnosis of [illegible]

DISEASE
IKW - MONOCLONAL ANTIBODY ACTIVATE CELL USEFUL VITRO DIAGNOSE BRAIN DISEASE DISEASE
INW - GHEUENS J; VANHEUVERS H
NC - 016
OPD - 1989-07-05
ORD - 1991-01-06
PAW - (INNO-N) INNOGENETICS SA
TI - Monoclonal antibodies against activated microglial cells - useful for in vitro diagnosis of brain diseases, e.g. alzheimer's disease